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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,206	12/12/2000	Trevor Douglas	50198-154	1984

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EXAMINER
PARKIN, JEFFREY S

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/09/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/734,206	Applicant(s) DOUGLAS, T., ET AL.	
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Detailed Office Action

Status of the Claims

1. Acknowledgment is hereby made of receipt and entry of the preliminary amendments filed 12 December, 2000, wherein claims 1-20 were canceled without prejudice or disclaimer and new claims 21-38 submitted.

Information Disclosure Statement

2. The information disclosure statement filed 12 December, 2000, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-38 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for compositions containing virion-constrained nanoparticles comprising a shell of a non-plant virion coat protein or methods of their preparation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The disclosure provides *in vitro* methods for reassembling CCMV viral coat proteins into empty particles. These particles were incubated with 0.4 M Na_2WO_4 to produce virion-constrained nanoparticles. Additional methods detailing the

preparation of empty CCMV virions followed by their incubation with WO_4^{-2} ions under conditions of varying pH, to allow controlled gating, were also provided.

The broadly recited claim language encompasses virion-constrained nanoparticles derived from any viral protein. However, there are a number of caveats that would preclude the skilled artisan from practicing the claimed invention as set forth below.

It is art-recognized that the mechanisms of viral assembly are complex and poorly understood (Dong *et al.*, 1993). Proper virion assembly often requires an orchestrated interaction between both viral and cellular proteins. As Dong *et al.* (1993) reported, "The nature of protein-protein interactions during retrovirus assembly is not well understood, and molecular genetic analyses of functional regions within the gag and env gene products are only beginning to provide information in this regard." The specification does not describe the preparation of virion-constrained nanoparticles from any other virus, excluding CCMV. However, the broadly recited claim language applies to a multitude of viral coat proteins, many whose role in virion assembly remains to be elucidated, obtained from any prokaryotic, eukaryotic, plant, protozoan, or virus-like particles. However, applicants have not set forth sufficient guidance in the specification pertaining to the identification or selection suitable viral coat proteins, purification protocols, reassembly protocols, gating conditions, and delivery procedures.

Moreover, the field of molecular nanotechnology is in it's infancy, and not surprisingly, there are a number of limitations concerning it's application. Kaehler (1994) reviews the state-of-the-art and concludes that while there are many potential applications for nanotechnology, these applications have yet to be realized. The author states (refer to first paragraph, page 1799) that "Today we are in the frustrating position of being able to design many things that we believe will work without being able to

build any of them." The author further discusses the future role that self-assembling proteins may play in nanotechnology.

Additional teachings from Douglas *et al.* (1987) review some of the caveats associated with developing effective nanoparticles for drug delivery. The authors conclude that several physicochemical characteristics influence the ability of nanoparticles to be targeted effectively to the target site. It was reported (refer to third paragraph, page 234) that "Particle size, shape, and number, together with surface charge and surface characteristics, all influence the biofate of colloids upon injection." Additional concerns arise from limitations associated with drug loading, drug release, nanoparticle toxicity, and the immunogenicity of the nanoparticle under study (refer to pages 245-251). Finally, the authors emphasize (refer to penultimate paragraph, page 255) that "Site-specific drug delivery using colloidal carriers is a highly complex area. Before further progress can be made, a greater understanding of the basic physiological and biochemical parameters will be required."

Douglas (1996) also provides any overview of the biomimetic synthesis of nanoscale particles in organized protein cages. A number of limitations have precluded the advancement of this field as set forth by the authors (refer to first paragraph, page 92) who stated that "There remain difficulties to overcome such as instability to particle aggregation, inhomogeneous particle size distributions, insolubility of host matrices, and an inability to extract the material from the host matrix." It was further reported that the only system that routinely provided reproducible results involved ferritin nanoparticles. However, the authors cautioned that only ferritin from a single source (e.g., equine spleen) had been routinely examined. Ferritins obtained from different sources may display different and unacceptable solution chemistry properties thereby obviating their use as nanoparticles. Moreover, the process of nanoparticle assembly involves several complicated steps including

oxidation, hydrolysis, nucleation, aggregation, and particle loading.

Finally, Houk *et al.* (1996) provide several concerns regarding gating as a control element for nanoparticle loading. The authors report that some host molecules have small portals that preclude guest or solvent passage through the molecule into the interior of the particle, other hosts have large portals that are not readily influenced and fail to form any stable complex with the guest molecule, and finally, some host molecules have small portals that admit guest molecules only under specific solvent conditions.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). In the instant application the specification fails to provide adequate guidance concerning a number of these considerations as they pertain to the claimed invention. The disclosure only provides a single working embodiment while the prior art clearly provides a number of rational scientific caveats (e.g., nanoparticle instability due to particle aggregation; inhomogeneous particle size distributions; insolubility of host matrices; inability to extract the material from the host matrix; and inability to control gating mechanisms) that would preclude the skilled artisan from practicing the claimed invention. Applicants fail to provide any guidance pertaining to any of these critical parameters. Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue

experimentation from the skilled artisan to practice the claimed invention.

Correspondence

5. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

6. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 O.G. 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242, (703) 305-3014, or (703) 308-4315. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

7. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 9:00 AM to 7:00 PM (Eastern Standard Time). A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the Examiner's supervisor, James Housel, can be reached at (703) 308-4027. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist at (703) 308-1235.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Technology Center 1600

27 July, 2002